- **Better explanation of what the sensitivity analysis shows.** The sensitivity analyses presented offer insight as to how the cancer potency estimates change as drinking water consumption and non-water arsenic intake assumptions change. The various non-water arsenic intake rate assumptions produced modest changes in risk, with the exception of bladder cancer risk in females. This calculated risk was very sensitive to the non-water intake rate assumption. The assessment and this analysis will be strengthened by providing a short explanation for why this is the case.

- **Need for better justified default assumptions.** Despite some effort to discuss drinking water consumption rates and sources of information for non-water arsenic intake rates, the reasons for some of the specific values chosen to be included in the sensitivity analyses are not clearly justified. For example, the "default" drinking water consumption rate for Taiwanese males is 3.5 L/day, citing precedent from U.S. EPA (1988), Chen et al. (1992), and NRC (1999 and 2001). For the sensitivity analysis, alternative values of 2.75, 3.0, and 5.1 L/day were evaluated [along with alternative values for Taiwanese females]. No rationale is provided for these specific numbers, other than they are thought by the agency to span a "reasonable range of values" (see page A-6). To enhance transparency in this example, it would be helpful to know the scientific basis for selecting the lowest and highest numbers (defining the range). Also, if the intent was to illustrate effects at the boundaries of the range of drinking water consumption rates, it is unclear why the lowest estimate for males (2.75 L/day) was not consistent with the lowest estimate for females (2.0 L/day) (see Table 5-10), especially given the SAB's request to justify different consumption values for men and women. Furthermore, no values for drinking water consumption rates for Taiwanese women were evaluated below the "default" rate of 2.0 L/day, suggesting that the value selected by the agency is at the limit of the range of reasonable values for this parameter. The effects on risk were determined based on assumptions that both the reference and exposed populations had non-water intake rates of 0, 30, and 50 μg/day arsenic. Although compliant with SAB's 2007 recommendations, better discussion of dietary intake of inorganic arsenic would help the reader understand whether the various values included in the analysis represent different interpretations of the existing data, bounding estimates, or something else.

- **Consider additional permutations of gender-specific water consumption.** The 2007 SAB recommended: "Because data on gender differences in consumption in Taiwan are limited, a better justification for assuming different consumption levels by gender is needed, particularly given the lack of sex difference in consumption in United States and observed in studies from other countries (Watanabe et al., 2004). In the absence of such a justification, the SAB recommends an additional sensitivity analysis to examine the impact of equalizing the gender-specific consumption level." The agency complied with this recommendation to some extent, evaluating the effect on risk of setting the drinking water consumption rate for both Taiwanese males and females at 2.75 L/day in the sensitivity analysis. However, the basis for the choice of this particular drinking water consumption rate is not explained. Also, by examining a single drinking water consumption rate for both sexes, the influence of selection of different rates on resulting risk is not illustrated. In order to be responsive to the 2007 SAB recommendation,

discussion of the impact of using a single drinking water consumption rate for males and females for the Taiwanese populations needs to be justified and expanded.

- **Need to clearly delineate the basis for water concentration assumptions.** Based on the data in tables 5-10 and 5-11, it isn't clear if EPA has completed the calculations that the SAB requested. Those tables noted that the sensitivity analyses used minimum and maximum village water arsenic concentration values. It isn't clear if only the villages with more than one well measurement were used or if all the villages were used. EPA needs to clarify the water concentration assumptions. This recommendation is also consistent with recommendations under charge question #2.

- **Need to address water consumption rates of susceptible groups.** The 2007 SAB recommended that the "EPA should evaluate the impact of drinking water consumption rates associated with more highly exposed population groups with potentially different exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure estimates as the agency determines the overall effects of drinking water consumption rates on arsenic risk." In the current 2010 draft IRIS assessment, the impact of drinking water consumption rates associated with more highly exposed population groups with potentially different exposures and susceptibilities (e.g. children, pregnant women) in its arsenic exposure estimates has not been evaluated. During the April meeting, the agency indicated that including these populations in the sensitivity analysis would be difficult and of limited value. So that the response to this 2007 SAB comment is clear, an explanation of why this aspect of the sensitivity analysis was not conducted should be included in Appendix A.

- **More complete and graphical analysis.** EPA has responded to the 2007 SAB's suggested sensitivity analysis with the development of Tables 5-10 and 5-11 along with Figure 5-2 showing the influence of various exposure assumptions including water arsenic concentration, non-water arsenic intake, and water consumption on various cancer endpoint risks. The tables and figure are efficient in providing a "snapshot" of their influence for various assumed point estimates; however, a more complete description of their influence can be shown by graphing across the range of plausible values. Admittedly, the graphical representation will be less efficient (i.e., require more space) but will provide a more complete depiction. To the extent possible, it would be useful to illustrate on these graphs the various historically and currently "assumed" values.

- **Testing the effects of layered assumptions.** To further respond to the 2007 SAB's recommendation, EPA tested the effects of changing assumptions one at a time. This approach is necessary to clearly show how individual values potentially affect cancer potency and risk. This approach does not, however, indicate how changes in assumptions might interact to produce overall changes in potency and risk. Testing all of the various permutations of changes in assumptions in a sensitivity analysis would be arduous and of dubious value. Nevertheless, it may be instructive to examine selected sets of exposure assumptions and their effect on cancer potency. This would provide an indication of the extent to which a reasonable range of exposure assumptions in the aggregate has the potential to affect cancer potency estimation.

- **Clarification of what the exposure assumptions are intended to represent.** It is often unclear in the assessment whether the exposure assumptions (e.g., drinking water consumption rate) selected are intended to represent best estimates of the mean for the exposed population, upper confidence estimates of the mean, upper percentile values, upper confidence limit estimates of an upper percentile value, or something else. This should be specified in the IRIS assessment. During the April meeting, the agency indicated that different types of assumptions may be appropriate for different values. The rationale for why a particular value is used should be provided in the IRIS assessment. For example, why an upper percentile drinking water ingestion rate is appropriate for the U.S. population, while an average (or upper bound average) assumption is used for the Taiwanese population.

- **The bases for the exposure assumptions selected are not adequately described.** The SAB in 2007 stated, "Much greater rigor needs to be applied in discussing and presenting documented data sources and making clear the basis on which assumptions are being made and the relative strength of those assumptions." That criticism applies to the 2010 version of the IRIS assessment as well. Some examples include:

    - For non-water arsenic intake, EPA has selected an assumed intake value of 10 μg/day. Discussion in support of this selection occurs on pgs. 123-124 of the revised assessment and is based on six references including US EPA (1989), Schoof et al. (1998), Yost et al. (1998), NRC (1999), NRC (2001), and EPA (2005c). Of these, there are only two references that relate to the peer-reviewed primary literature, reflecting the scarcity of data from which to base this estimate. Although EPA does a reasonable job of discussing these reports, the current assessment lacks a specific rationale or justification for the selected value. It appears that the US EPA 1989 reference supporting an intake range of 2 μg/day to 16 μg/day may provide the rationale for this selection. Since this reference is not easily available, the SAB recommends that within the IRIS assessment a more complete discussion of data and evidence supporting this intake range be provided in a manner similar to what has been provided for Schoof et al. 1998 and Yost et al. 1998. In the current assessment, it is unclear what the 2 to 16 μg/day estimate is based on. Moreover, the current assessment does not provide a specific justification or rationale for this selection, but rather makes a broad statement "Based on available information, EPA selected 10 μg /day as the best estimate for non-water arsenic intake (food sources) in baseline calculations." The selection of this value can be strengthened by: 1) elaborating on the lack of data or evidence upon which to base this estimate; 2) distinguishing between evidence that is primary (i.e., peer-reviewed with data collection) and reports that provide expert assessment, and 3) providing specific and scientific justification for the selected value that can be traced to the primary literature. Again, because of the effect this parameter has on the risk estimates, providing support for the values chosen for this parameter is important.

    - The current dose-response assessment is based on an assumed water intake value of 3.5 and 2.0 L/day for men and women, respectively. As with the assumed values for

non-water intake above, justification for these values can be strengthened by establishing a clear link to data within the primary literature where possible. The specific relevant findings from Chen et al. 1992 and Chowdhury et al. 2001 should be provided in relation to the selected values. In the current assessment, it appears that EPA justified the selected values largely based on precedent (e.g., EPA and NRC reports) rather than on the data reported in the primary literature. It is unclear why EPA did not base their estimate on the data of Chowdhury et al. 2001 since it is unique and relevant. No discussion is provided of the data available from Chen et al. 1992. To the extent that EPA relies on previous EPA and NRC assessments, the link to the primary data (if available) should be maintained. The problem illustrated by the 2010 assessment is that these assumed values take on a life of their own and the evidence upon which they are based is lost, i.e., the scientific basis for the assumptions is no longer discernible.

- **The reason for limiting non-water intake to dietary sources is not explained.** Non-water exposure is currently assumed to consist entirely of arsenic in the diet. For completeness and transparency, EPA should provide a short description of alternate routes of exposure (e.g. inhalation, non-dietary ingestion, dermal absorption) from other media such as soil and include arsenic intake estimates using EPA's routine exposure assumptions for both the Taiwan and the U.S. populations; EPA should provide justification for why these other exposures were not considered in the current dose-response assessment. If the reason is that other pathways are assumed to be minor relative to arsenic intake from diet, some illustration of this should be provided as justification.

Other Comments

- **More clear delineation of organic vs. inorganic exposure assumptions.** It would be helpful to provide a paragraph for IRIS users explaining why the organic arsenic compounds do not affect the risk estimates for inorganic arsenic. The explanation will probably be fairly straight forward for the seafood organic arsenic compounds. This may not be as straight forward for any organic arsenic compound in produce (e.g. rice, etc.). As a related comment, when discussing non-water arsenic intake care should be taken to distinguish between inorganic and organic or total arsenic in food. The current draft assessment is in some places ambiguous, referring simply to "arsenic." (see pages 123-124).

- **Value in identifying research gaps.** Given the importance and scarcity of data for purposes of estimating exposure, the SAB suggests that EPA provide a short paragraph describing the research needs along with suggested designs to produce credible estimates for water and non-water intake rates. The research needs are not only to provide point estimates, but data for distribution analysis to support the more credible stochastic approaches to risk estimation. Maybe 10 years from now, we will not find ourselves in the position that we are in now of relying on largely the same sparse/inadequate data for risk estimation that we were in 10 years ago.

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APPENDIX A - Minor edits

- Pages 139 and 140: Providing some information in these tables about the range in village water arsenic concentrations would be useful.
- Type in footnote for Table 5-11. Table 5-8 should probably be Table 5-10.
- Page 141, line 27. Tables 5-6 and 5-9 should be Tables 5-10 and 5-11
- Page 142 – line 3. Should both increased and decreased be there?

NIEHS
National Institute of Environmental Health Sciences

The Role of NIEHS/NTP Science in Regulatory Decisions

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health Sciences
National Toxicology Program

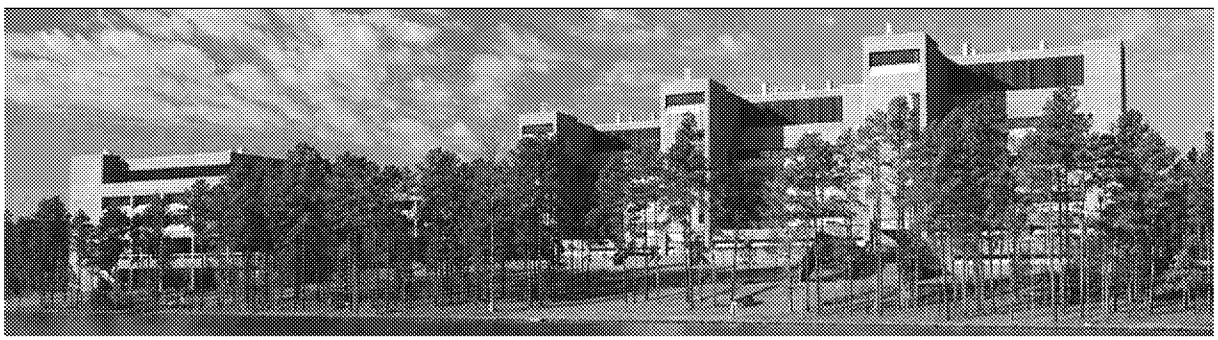
Pew Charitable Trusts
Washington, DC
April 5, 2011

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIEHS
National Institute of Environmental Health Sciences

National Institute of Environmental Health Sciences

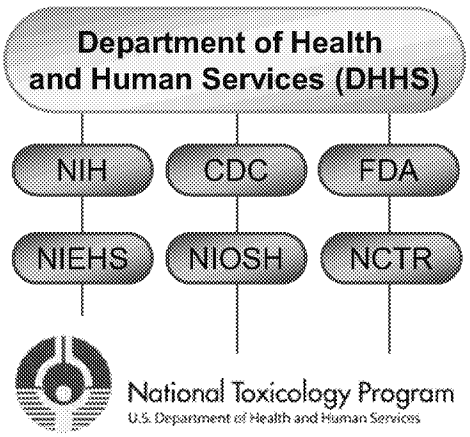
- **One of the National Institutes of Health, but located in Research Triangle Park, NC**
- **Wide variety of programs supporting our mission of environmental health:**
  - **Intramural laboratories**
  - **Extramural funding programs**
  - **National Toxicology Program**
  - **Superfund Research and Worker Education and Training Programs**



NIEHS
National Institute of Environmental Health Sciences

National Toxicology Program

- Interagency program
  - Established in 1978 to coordinate toxicology research across the Department of Health and Human Services (DHHS)
  - Headquartered at NIEHS
- Research on "nominations"
  - Thousands of agents evaluated in comprehensive toxicology studies
  - Results communicated through technical reports, scientific publications and the web
- Analysis activities
  - Report on Carcinogens (RoC)
  - Center for the Evaluation of Risks to Human Reproduction (CERHR)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)



http://ntp.niehs.nih.gov

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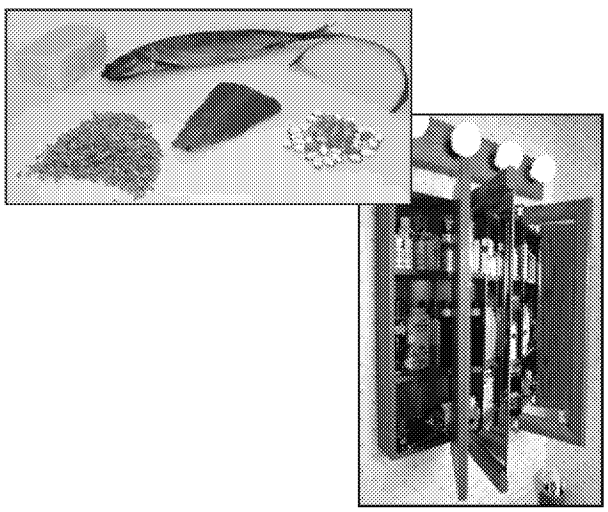
NTP Science for FDA

- NTP studies referenced in 52 notices / rules between 1982-2009
- Various items include acrylamide, skin-bleaching products, new animal drugs, OTC human laxatives, irraditaion of food, and food additives
- Food additives include:
  - food colorings
  - olestra
  - acesulfame K
  - adjuvants
  - acacia (gum arabic)



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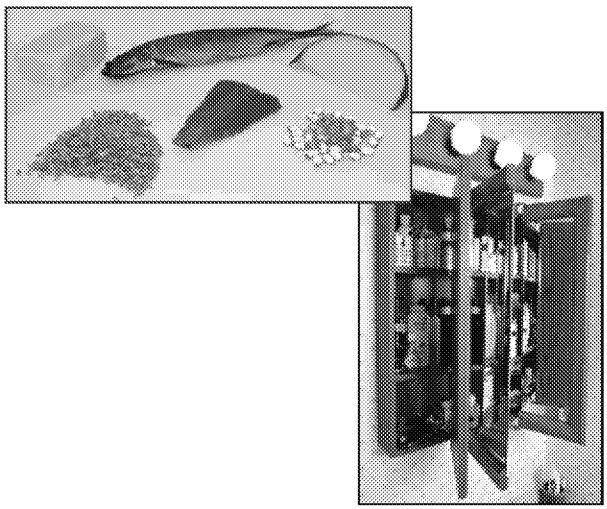
NIEHS Extramural Science for FDA

- Extramural grants produce substantial scientific output
- "Hypothesis-driven" studies provide equally good science
- NIEHS funded studies look at:
  - bisphenol A
  - nanotoxicology
  - phthalates
  - food additives
  - endocrine disruptors



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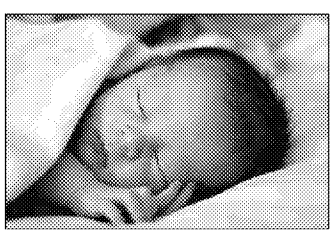
"ENVIRONMENT" Includes:

- Industrial chemicals
- Agricultural chemicals
- Physical agents (heat, radiation)
- By-products of combustion and industrial processes (dioxin)
- Foods and nutrients
- Prescription drugs
- Lifestyle choices and substance abuse
- Social and economic factors



NIEHS
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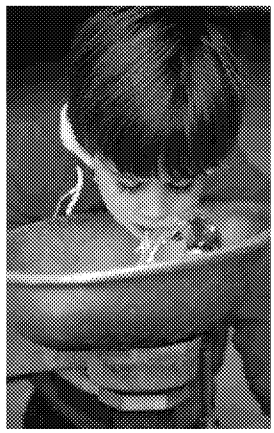
Diseases with a Known or Suspected Environmental Component Include:

- Cancers
- Birth defects (cleft palate, cardiac malformations)
- Reproductive dysfunction (infertility)
- Lung dysfunction (asthma, asbestosis)
- Neurodegenerative diseases (Parkinson's)
- Neurodevelopmental disorders (autism)



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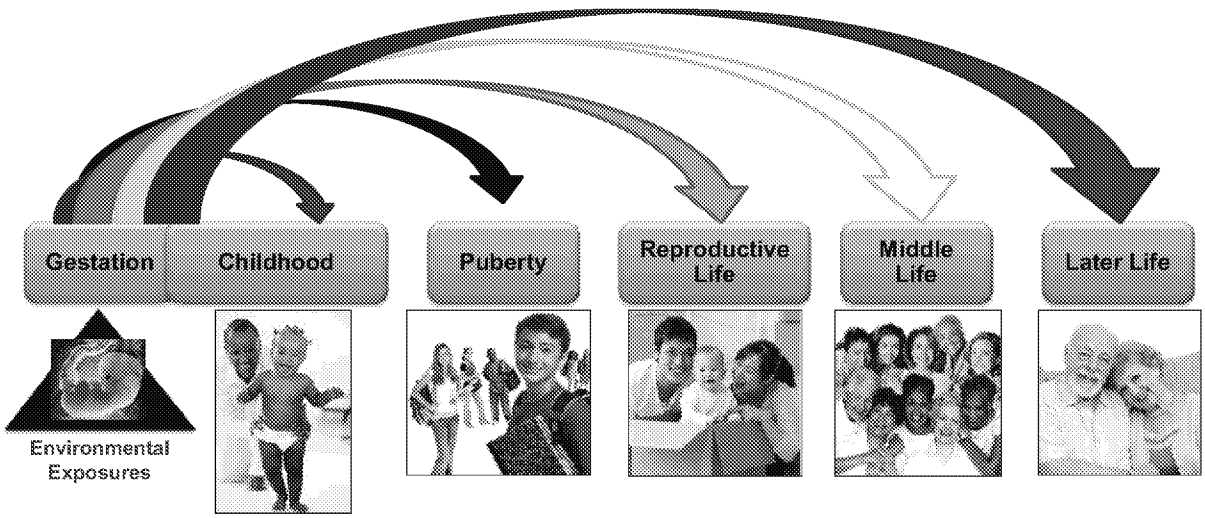
Developmental Origins of Disease:
Developmental Stressors Lead to Disease Throughout Life



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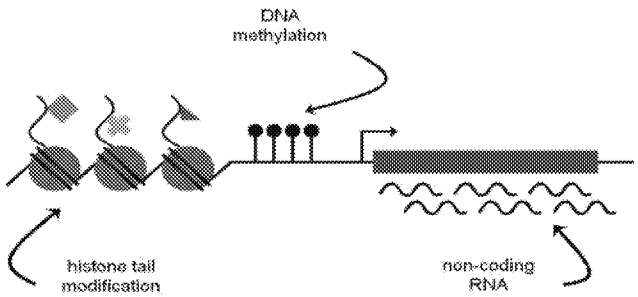
Epigenetics

- Inheritable modifications of chromatin and DNA expression
- Affect genome function (transcription, replication, recombination) but don't affect DNA backbone
- Developmental period is most sensitive to epigenetic alterations that persist throughout life
- Developmental exposures alter epigenetic marks, leadir to functional changes, leading to disease later in life.



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Neurodevelopment

- Neurodevelopment begins before birth and continues throughout childhood
- Chemicals can affect brain at any point during this development
- Chemicals, even in low doses, can cause significant, sometimes permanent harm
- Vast majority of chemicals in commerce are untested for their impacts on neurodevelopment

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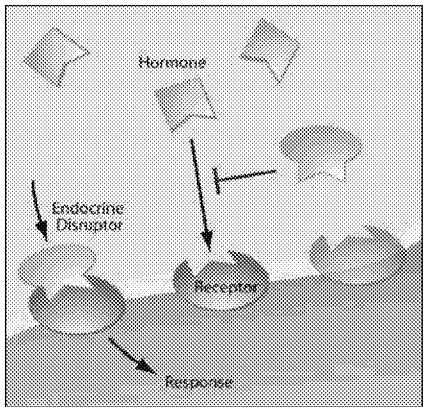
Endocrine Disrupting Chemicals

- Low dose
- Wide Range of Health Effects
- Persistence of Biological Effects
- Ubiquitous Exposure



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Risk = Hazard + Exposure

- Hazard is an important aspect of risk
- Exposure is equally important
- Mixtures present a challenge
- Exposures do not occur singly
- Research should account for mixture effects
- Routes of exposure must also be taken into account
- Internal Dose also important

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Good Laboratory Practices

- Should we rely on GLP studies?
- GLP (or any guideline) doesn't guarantee a good study
- GLP doesn't guarantee that the right question was asked
- Quality Assurance (QA) important
- A single study never truly answers all the regulatory questions
- Make sure that the best available science is utilized and incorporated in our understanding of risk

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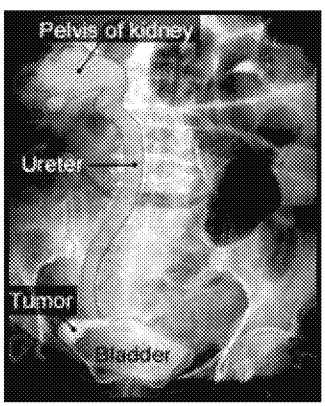
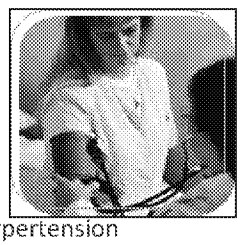
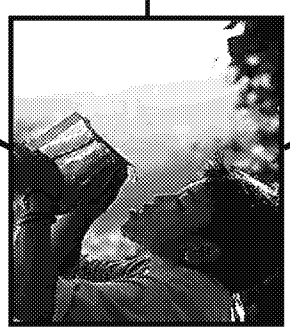
EPA's Arsenic Standard

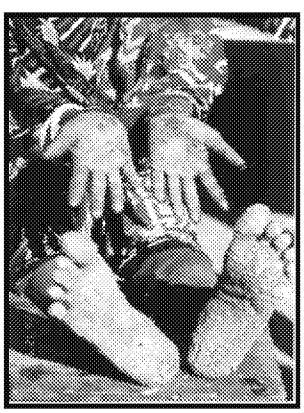


Bladder Cancer
Liver Cancer
Kidney Cancer



Hypertension
Developmental effects
Diabetes





Skin Cancer
Keratosis
Melanosis
Blackfoot Disease

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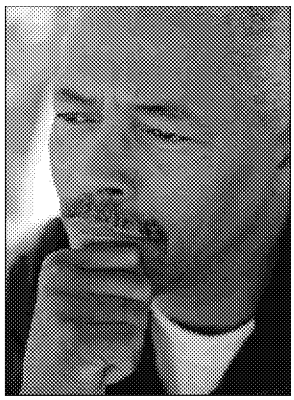
Conclusion

- NTP provides science directly for regulatory purposes
- NIEHS grantees also provide basic understanding and new insights
- Biological systems are incredibly complicated
- Multiple important endpoints
- Risk = Hazard + Exposure
- Regulatory framework must incorporate all available data



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Thank you!

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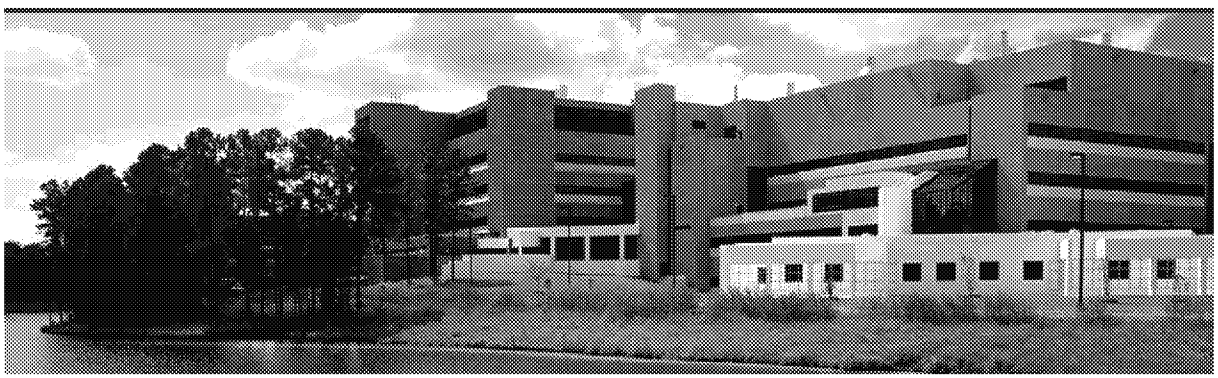
National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

SRP
Superfund Research Program

NIEHS Strategic Plan

NIEHS Strategic Plan Website
http://www.niehs.nih.gov/strategicplan



PEW Workshop on Regulatory Science

FDA's Safety Assessment Process for Food Additives and Use of Computational Toxicology

Mitchell Cheeseman, Ph.D.

Acting Director
Office of Food Additive Safety
April 5, 2011

Presentation Outline

- Overview of OFAS Responsibilities and Regulatory Processes.
- Elements of the Food ingredient/packaging safety assessment processes
  - Use and importance of guidance
  - Computational toxicology and the safety assessment process

The Food "Ingredient" Universe

Direct Food Ingredients:
Sweeteners; preservatives; nutrients; fat substitutes; texturizers (e.g., thickeners, emulsifiers); flavors

Color Additives: In food, animal feed, drugs, cosmetics, and medical devices (e.g., sutures, contact lenses)

Food Irradiation Equipment:
To Process food or to inspect food

GRAS Substances: Enzymes; fibers; proteins; lipids; sugars; MSG; antimicrobials; phytosterols/stanols; flavors; infant formula ingredients

Food Contact Substances:
Coatings (paper, metal, etc.); new/recycled plastics including polymers and monomers; paper; adhesives; colorants, antimicrobials, and antioxidants in packaging; packaging materials used during food irradiation; packaging "formulations"

Processing Aids: Antimicrobials (meat and poultry processing); defoamers; ion exchange resins

Foods/Ingredients Produced Via Biotechnology: Plants w/ herbicide resistance or insect resistance; delayed ripening, etc.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Comparison of the regulatory approaches for various food ingredients.

Petition Process	GRAS Notification	FCS Notification
For food additives since 1958 and for color additives since 1960	1997 to now (previously a GRAS affirmation petition process)	Since 1997 (previously handled as "indirect" food additive petitions)
Mandatory	Voluntary	Mandatory for food contact substances that are food additives
Industry submits a petition asking FDA to issue a regulation	Notifier informs FDA of their view that a use of a substance is GRAS	Industry submits a notification
FDA owns the safety decision	Notifier owns the safety decision; FDA evaluates the notifier's basis	FDA owns the safety decision but there is a 120-day "hammer"
FDA publishes a regulation	FDA responds by letter (no questions, no basis, withdrawal)	FDA responds by letter (deficiency, effective, objection)
Petition is available publicly through FOIA	FDA responses, and more recently entire GRAS notices, are published on FDA's website	FDA maintains a database of effective notifications on its website

Safety and Review Standards

- Standard of safety
  - Reasonable certainty of no harm
- Standard of review
  - Fair evaluation of all of the data

These standards are the same for food and color additives, GRAS substances, and food contact substances.

Safety Decision

- **Standard of Review**
  - **Fair Evaluation of the Data**

From the legislative history, "… should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial without taking account of the contradictory evidence of equal or even greater substance …"

Safety Decision

- **Safety Standard**
  - **Reasonable Certainty of No Harm**

From the legislative history:

The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive...."

"It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance."

H.R. Report No. 2284, 85th Congress 1958

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Harm Is Not Defined in the FD&C Act

- Although the concept of "harm" is central to the act's safety standard, neither the statute, nor regulations implementing the food additive provisions, define harm.
- However, Congressional intent is clear from the legislative history of the 1958 amendment.
- The legislative history reflects that an effect is harmful if it affects health, not if it is simply an undesirable or unexpected effect that has no adverse health consequences.

SAFETY DECISION

- Must protect public health by addressing the probative questions associated with the intended use.
- A consensus decision based on a fair evaluation of all the available data.
- Made with some level of uncertainty.
- Decisions are time-dependent.
- Must withstand scientific, procedural, and legal challenge from all sides.

Contents of a Food Additive Submission

- Identity and composition of the food ingredient.
- Manufacture and specifications.
- Use in food must consider -
  - Types of foods,
  - Levels in those foods, and
  - Intended effects.
- Estimated Daily Intake (EDI).
- Analytical methodology.
- Full reports of safety data, including toxicological and other studies – Acceptable Daily Intake (ADI).
- Proposed tolerances, if needed.
- Environmental information.

Chemistry Data and Information

Identity
- Chemical Name and CAS Number
- Structure and Molecular Weight
- Physical Characteristics

Manufacturing Process
- Full description of process
- List of chemicals/reagents used

Specifications
- Typically proposed by petitioner or reference published specs (FCC)
- Should include description of the additive, identification tests, purity assay, and limits for impurities/ contaminants

Stability
- Data demonstrating the stability
- Discussion of the fate of the additive

Technical Effect and Use
- Type of food and use level
- Data to show that the use level accomplishes the technical effect

Analytical Methodology
- If a use limitation of the additive is required for safe use, the petition must include a method able to quantify the substance for the purpose of enforcing the limit

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Elements of Review

- Manufacturing process, identity, purity and specifications
- Estimated Daily Intake to substance and impurities
- Consideration of adequacy of methods needed to ensure safety of the intended use
- Identification of any controls, specifications, or other limitations that are necessary to ensure safety

Assessment of Dietary Intake

- Estimate of dietary intake by consumers to the food additive (and by-products of concern) resulting from eating food(s) containing the additive.
- Petitioner provides an estimate, which OFAS confirms.
- Calculated as an estimated daily intake (EDI)
  - Assumes chronic or average daily intake over a lifetime, and
  - Is typically calculated for the mean and 90th percentile consumer.

Typical Toxicological Studies

- Short-term tests for **genetic toxicity** (in vivo and in vitro testing).
- **Metabolism** and **pharmacokinetic** studies.
- **Subchronic feeding studies** (at least 90 days) in a rodent (e.g., rat) and non-rodent (e.g., dog) species.
- Two-generation **reproduction** study with a teratology phase (developmental toxicity study) in a rodent (e.g., rat).
- **Chronic feeding studies** (at least one year) in a rodent (e.g., rat) and non-rodent (e.g., dog) species (may be conducted as a component of a lifetime carcinogenicity study in rodents).
- **Two-year carcinogenicity** studies in two rodent species (e.g., rats and mice). The rat carcinogenicity study should also include an *in utero* phase.
- Other studies as needed (e.g., **neurotoxicity** and **immunotoxicity**) based on available data and information about the substance.

The Redbook

- Criteria for evaluating the safety of food and color additives are in 21 CFR 170.42 and 70.20, respectively.
- These were considered too general to provide meaningful guidance to the public.
- The Redbook set out to -
  - Describe how existing information is considered and how the need for additional studies is assessed, and
  - Provide rigorous protocols for commonly used toxicology studies.

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FDA Guidance

- Guidance is not binding on FDA or the public
- Any and all other methods are acceptable to the extent that they address the same probative questions
- By regulation, FDA guidance documents are always open to public comment

21 CFR 10.115(g)

Other Guidance and Guidelines

- EPA - http://www.epa.gov/
- EFSA - http://www.efsa.europa.eu/
- FSANZ - http://www.foodstandards.gov.au/
- JECFA - http://www.who.int/ipcs/food/jecfa/en/
- OECD - http://ntp-apps.niehs.nih.gov/iccvampb/OECD.cfm
- Health Canada - http://www.hc-sc.gc.ca/index-eng.php

This is certainly not an all inclusive list; there are many other valuable documents relevant to food ingredient safety used by FDA scientists and technical reviewers.

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Elements of Review

- Review of safety studies presented in a submission or available in the public literature to identify relevant studies
- Evaluation of relevant safety studies to determine adequacy of the data set to support estimated exposure
  - Guidance is a starting point to determine data needs
  - Evaluation of the rigor of the study for risk/safety assessment
  - Identification of any additional questions raised by data
  - Determination of a safe exposure level (ADI)

STUDY REVIEW CRITERIA

- Administration (route of)
- Sample size and statistical analysis
- End-point(s) measured
- Plausibility
- Dose response
- Gender effects
- Repeatability
- Environmental contamination

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Source of the Study

- Is irrelevant
- FDA applies the same criteria in weighing a study without regard to whether the study comes from academia, government, or industry
- The criteria apply to the design and conduct of the study, not to the source

The Use of Computational Toxicology

- Enables a fast systematic review
  - To identify relevant data
  - To characterize that data within our knowledgebase
- Provides tools and an approach to incorporate newer testing
  - Enabling the use of high throughput and other data to biologically map compounds
  - Enabling the analysis of such biological profiles in relation to our knowledgebase
- Allows characterization of relative activity of compounds
  - Based on more traditional toxicology data
  - Greatly enhanced with the inclusion of higher throughput “toxcast” type data

(Q)SAR Software

- ToxTree (EC-Joint Research Centre)
- OncoLogic (EPA)
- Derek for Windows
- MultiCase
- MDL QSAR
- Leadscope Model Applier
- Advanced Chemistry Development (ACD) Labs
- BioEpisteme (Prous Institute)
- SciQSARTM (Scimatics)
- ADMET Predictor, GastroPlus MedChem (Simulations Plus)

References to commercial products in this presentation do not constitute an endorsement by the US FDA.

Toxicity Databases

- Commercial
  - Leadscope (site license)
    - FDA CFSAN
    - FDA CDER
    - Public databases (ToxCast, DSSTox, RTECS)
  - Vitic (ten licenses)
    - FDA CFSAN
    - FDA CDER
    - Public data
    - Industry data
- Public
  - ChemID Plus
  - ToxNet
  - DSSTox
  - CPDB

References to commercial products in this presentation do not constitute an endorsement by the US FDA.

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Uses of Computational Toxicology Tools

- Structurally searchable databases
  - Carcinogenicity
  - Genetic Toxicity
  - Reproductive Toxicity
  - Subchronic Toxicity
- Predictive modules
  - Carcinogenicity
  - Genetic Toxicity
  - Teratogenicity

Impact and Uses of Computational Toxicology

- Supplement limited data
  - Inconclusive tests
  - Tests that would not ordinarily be submitted
- Analog identification and assessment
  - Can supplement data an the compound of interest
  - Can assist in characterizing an untested compound in "toxicity space"
- Identify compounds of potential concern at levels below those recommended for testing

(Q)SAR Case Study

- Oxygen scavenger for PET
- Low exposure
  - FCS < 4 μg/p/d
  - Impurity < 0.6 μg/p/d
  - Suspected potential developmental toxicity
  - No developmental data available

(Q)SAR Case Study

- Structure Analog
  - Structure similarity search using Leadscope Enterprise and ChemID- Plus returned no analogs
  - Search performed on phthalimide and isoindol-1-one substructure to identify additional safety data

(Q)SAR Case Study

- Substructure search identified numerous chemicals containing the phthalimide and isoindol-1-one substructure
- Literature contains mixed results on the teratogenicity of related query compounds from highly potent to inactive

(Q)SAR Case Study

- SAR results inconclusive on safety of materials
- Recommendation: a teratogenicity study with most sensitive species (Himalayan rabbit, 20 does/group, full scale macro- and microscopic examinations)
- No treatment-related effects found in study

CFSAN's Risk Management Framework

- Risk analysis includes risk management.
  - Process of weighing policy alternatives and implementing appropriate control options, including regulatory measures.
- CFSAN's risk management framework addresses –
  - How input from risk assessment is applied to take actions which are appropriately protective of public health; and,
  - How the outcomes of decisions are monitored and re-evaluated.

European Food Safety Authority

Chemical risk assessment in EFSA: Current and future activities

Jean Lou Dorne
Emerging risks unit
http://efsa.europa.eu

Content

European Food Safety Authority

- EFSA's mission and work
- Chemical risk assessment in EFSA
- Current and future horizontal activities

EFSA and EFSA's mission

- EFSA is the European Union's scientific risk assessment body on food and feed safety, nutrition, animal health and welfare, plant health and protection, tackling issues all along the food chain. **Regulation (EC) 178/2002**
- Provide science based risk assessments supporting risk management related to food/feed safety.
- Provide scientific and technical advice on all matters within these fields.
- Communicate all findings publicly.

EFSA's structure

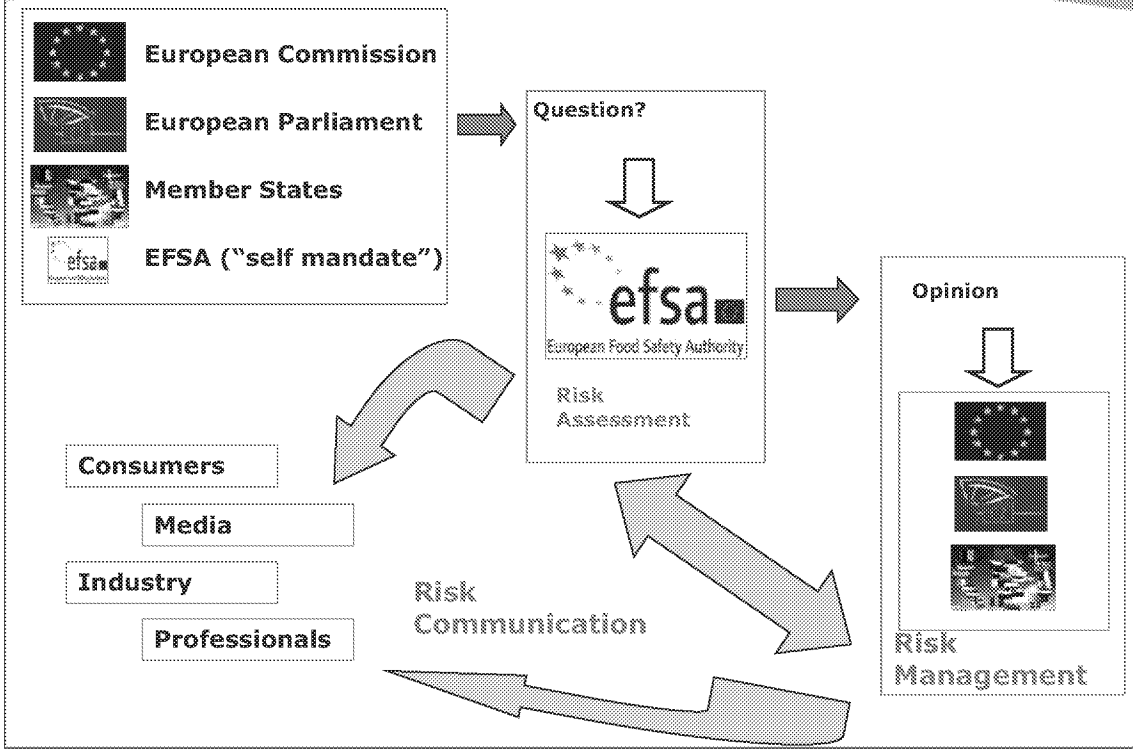
Management Board + **Advisory Forum**

\+ \+

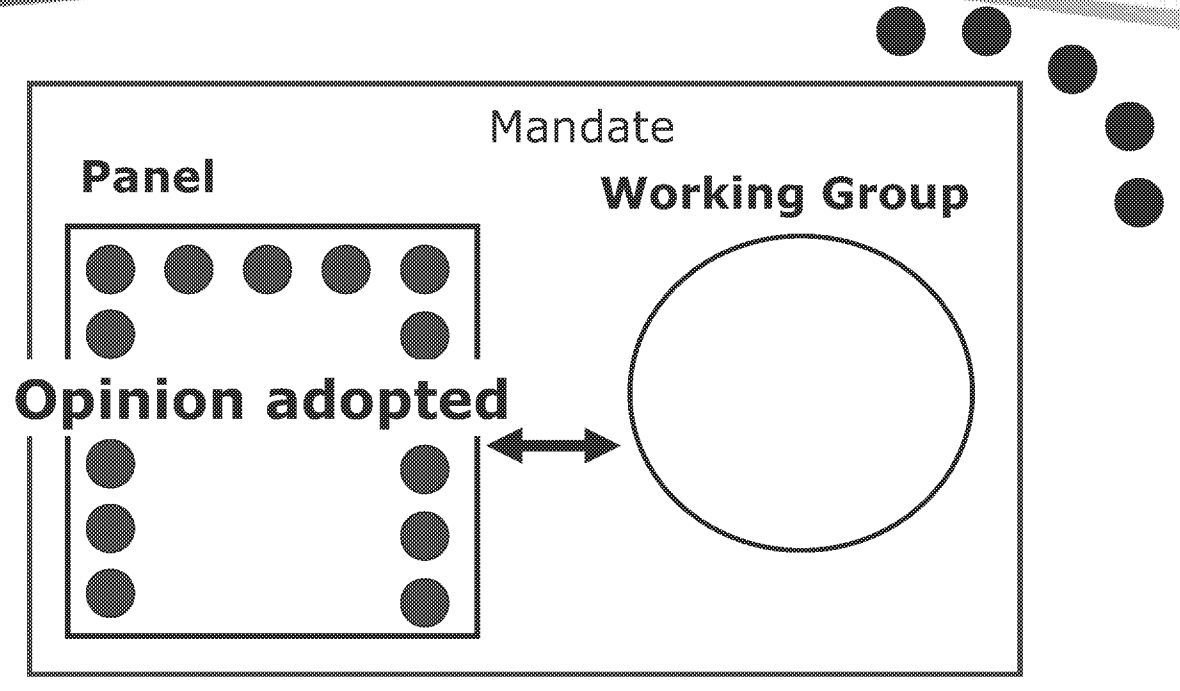
EFSA Staff **Scientific Committee and 11 Panels**

= efsa European Food Safety Authority

How does EFSA work ?

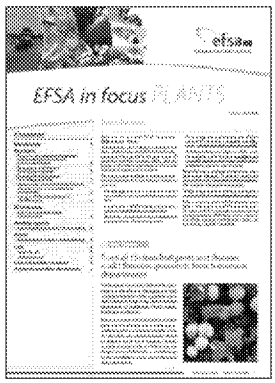


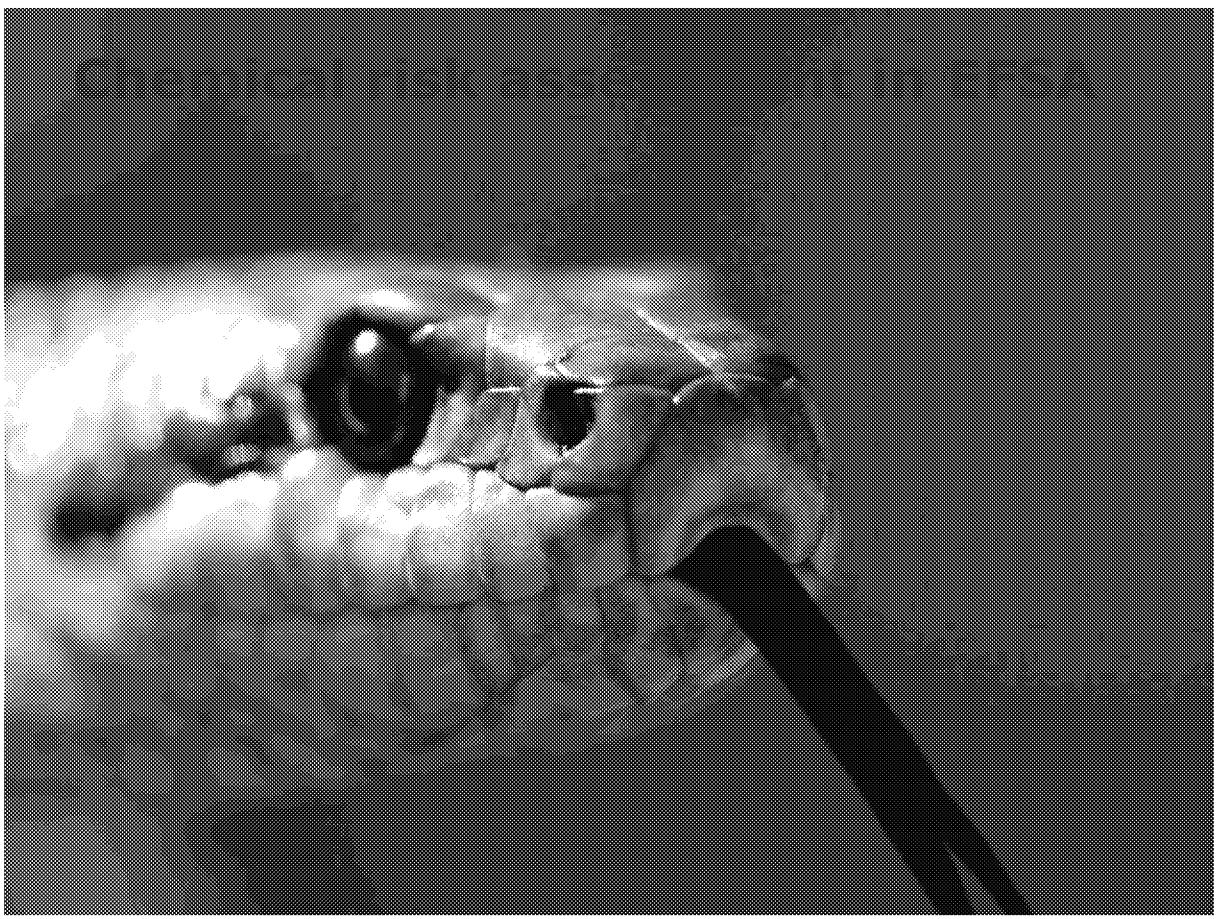
How does an EFSA opinion get adopted ?



How does the Science is communicated to the public ?

efsa
European Food Safety Authority

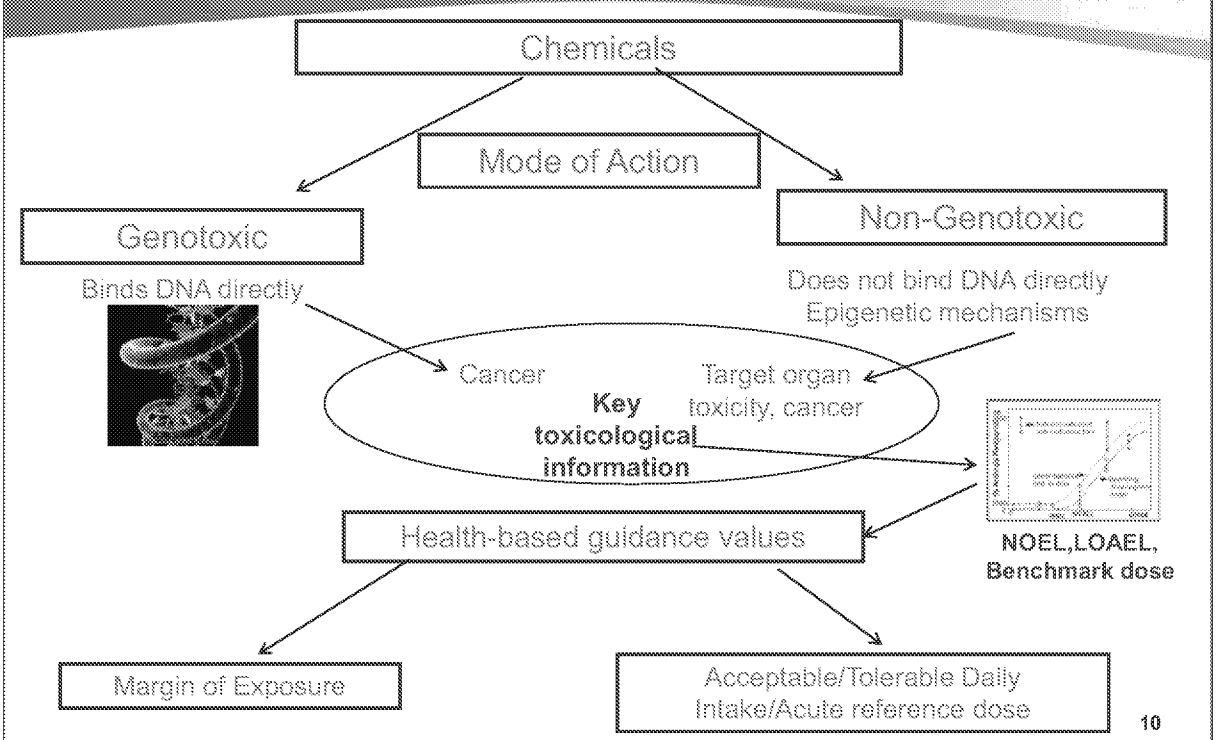


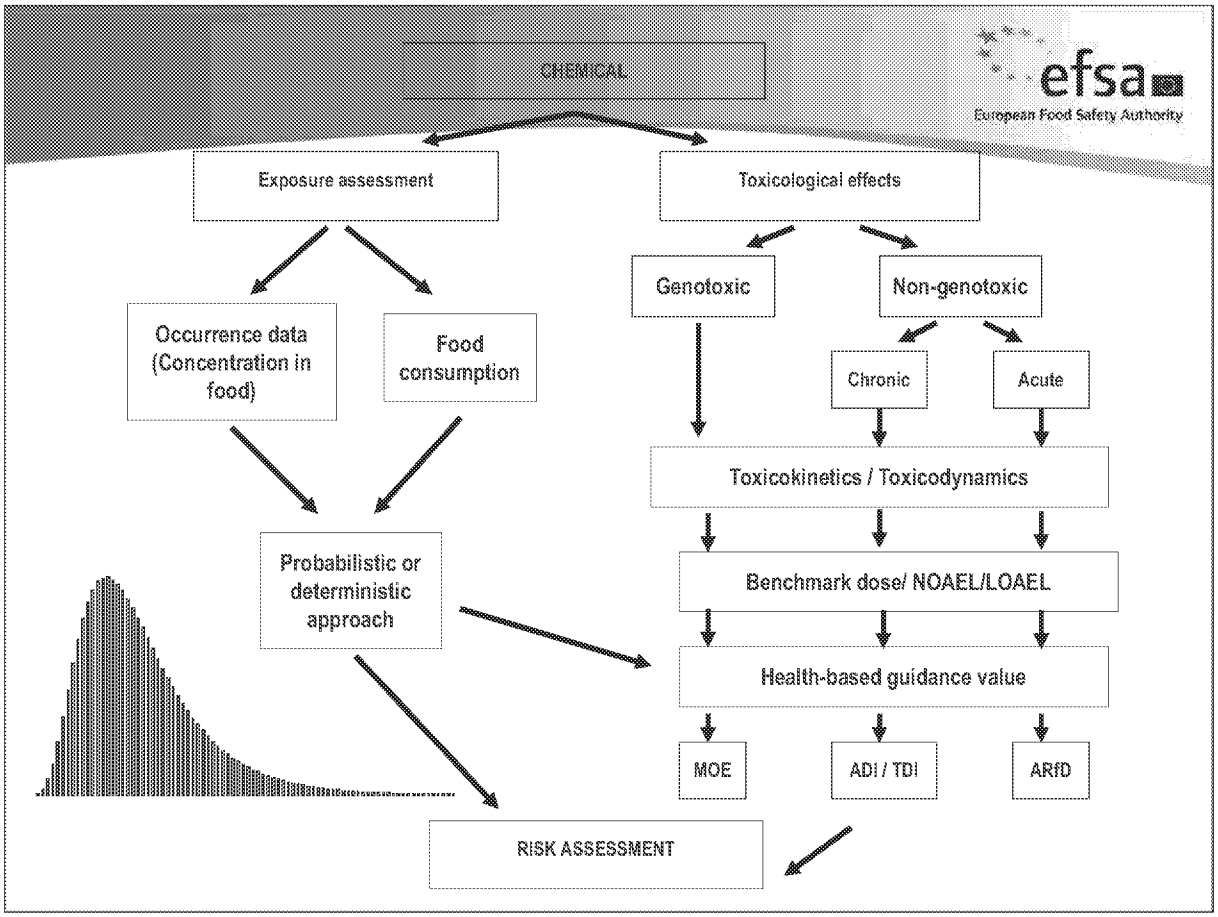


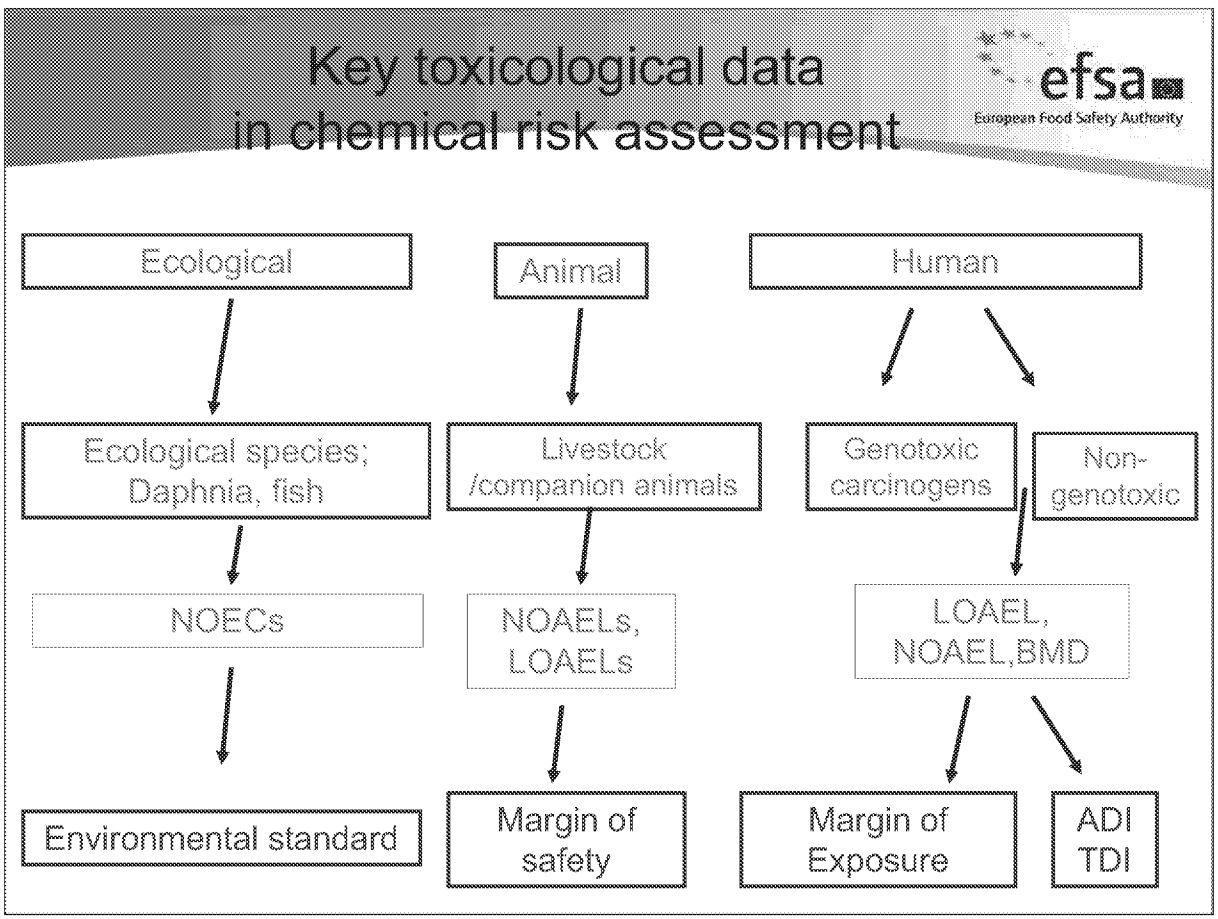
Key Chemicals assessed in EFSA

- Contaminants
- Plant protection Products
- Vitamins and minerals
- Food additives and nutrient sources
- Feed Additives
- Food contact materials, enzymes,
- Flavourings and processing aids
- Proteins used in GMOs

Chemical risk assessment at EFSA




CHEMICAL
efsa
European Food Safety Authority
Exposure assessment
Toxicological effects
Occurrence data (Concentration in food)
Food consumption
Genotoxic
Non-genotoxic
Chronic
Acute
Toxicokinetics / Toxicodynamics
Probabilistic or deterministic approach
Benchmark dose/ NOAEL/LOAEL
Health-based guidance value
MOE
ADI / TDI
ARfD
RISK ASSESSMENT


Key toxicological data in chemical risk assessment
efsa
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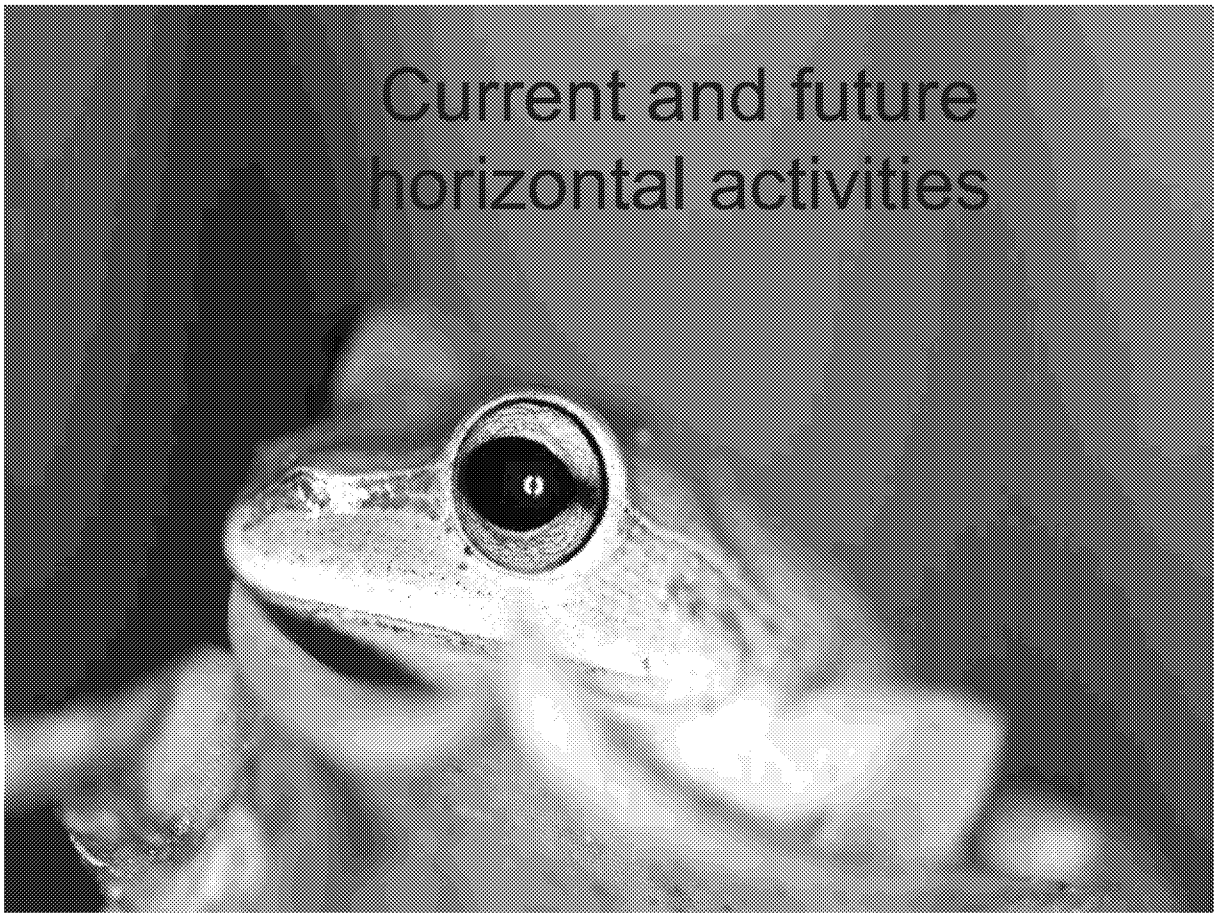
Ecological
Animal
Human
Ecological species; Daphnia, fish
Livestock /companion animals
Genotoxic carcinogens
Non-genotoxic
NOECs
NOAELs, LOAELs
LOAEL, NOAEL,BMD
Environmental standard
Margin of safety
Margin of Exposure
ADI TDI



Identification of Emerging Risks

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- Identifying emerging risks is a fundamental task of EFSA
- EFSA Scientific committee opinion on identification of emerging risks (July 2006)
- Formal adoption of the *definition of emerging risks* (Aug 2007):

  New hazards or known hazards with an increased exposure or increase susceptibility to known hazards
- EFSA's Emerging Risks Unit established in 2008
- Strategy: scientific literature, commission, member states, experts, media monitoring
- Projects: monitoring/ identifying biological and chemical emerging risks, methodology and data collection, chemical hazards database, chemical mixtures/consumption of energy drinks in the EU

Rapid/urgent risk assessments in EFSA

- Requests from the European Commission: one-two days to perform the risk assessment and publish it including communication to the public

Examples

- 2007-Melamine in pet food
- 2008-Mineral oil in sunflower oil from Ukraine

  -Melamine in milk and derived products from china

  -Dioxin in meat products
- 2009- Nicotine in mushrooms
- 2010-Volcanic ashes after volcanic eruption in Iceland

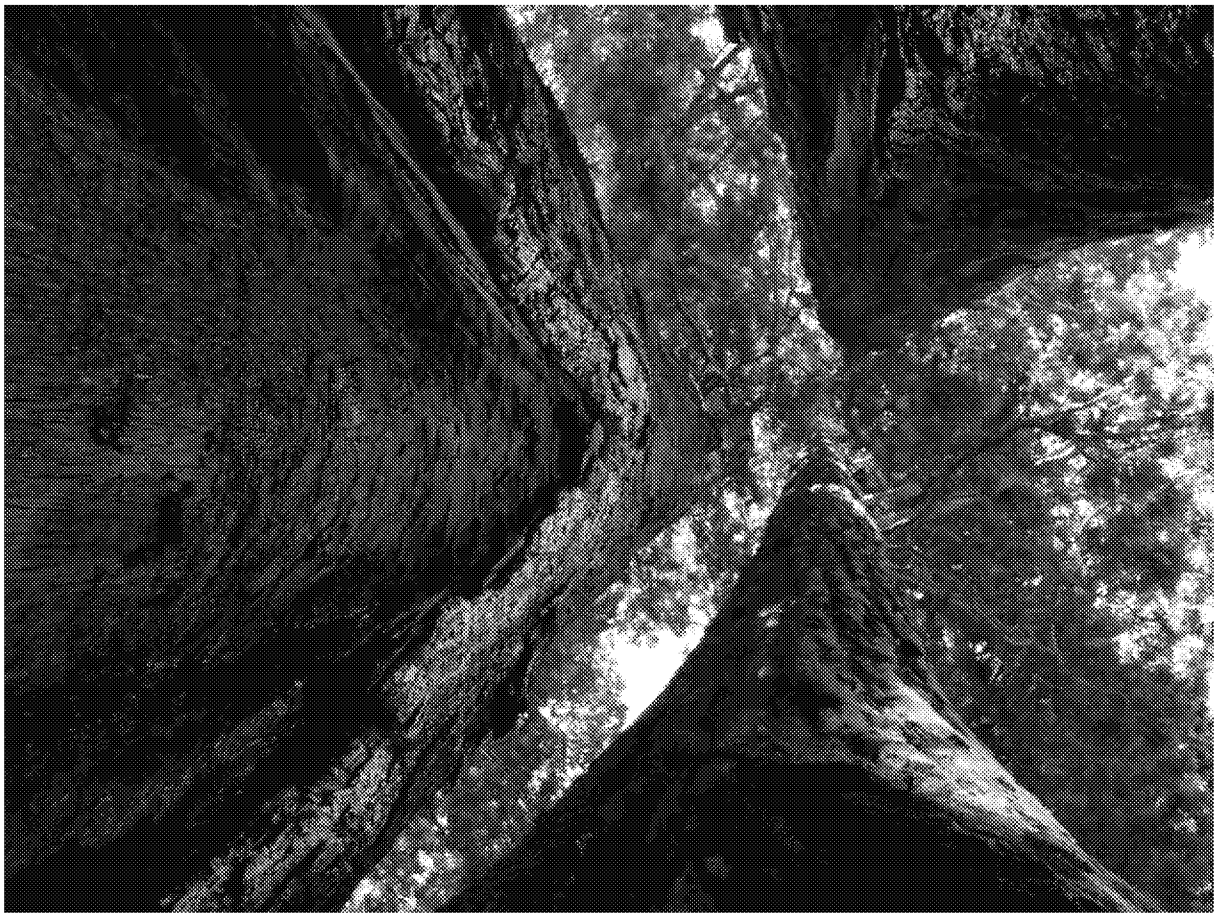
Chemical Hazards Database

❖Database providing holding key information for all chemical hazards assessed by EFSA for food and feed (ecological species, animal, human health).

❖Design take into account other ongoing databases and other international agencies (ECHA, OECD, WHO, US-FDA, US-EPA) to exchange data and harmonise database format/ structure to international standards (ideally within IUCLID)

❖Will also include hazard data from other international organisations (SCF, SCAN, ECHA, WHO, US-FDA, US-EPA…)

•Deliver database including an online application-December 2012



Scientific committee 2009-2012
Examples of activities

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- Applicability of the Threshold of Toxicological Concern
- Nanomaterials and nanotechnologies (EC)
- 90-day toxicity test on complex food and feed items (EC)
- Harmonisation of genotoxicity testing strategies (self task)
- Discussion on endocrine active substances & environmental risk assessment (self task)
- Development of guidance on statistical approaches (self task)

Current and future activities

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European Food Safety Authority

- **Methods for risk assessment of chemical mixtures**

-Panel on pesticide and their residues applying methodologies to classify pesticides according to their mode of action for cumulative RA

-Activities in the IPCS working group on chemical mixtures WHO
-Internal task force exploring available frameworks (WHO, OECD, US-EPA…)

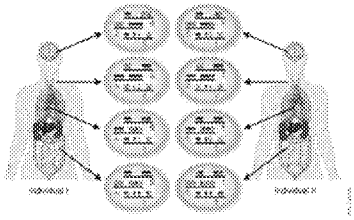
- **Applicability of new methodologies in risk assessment**

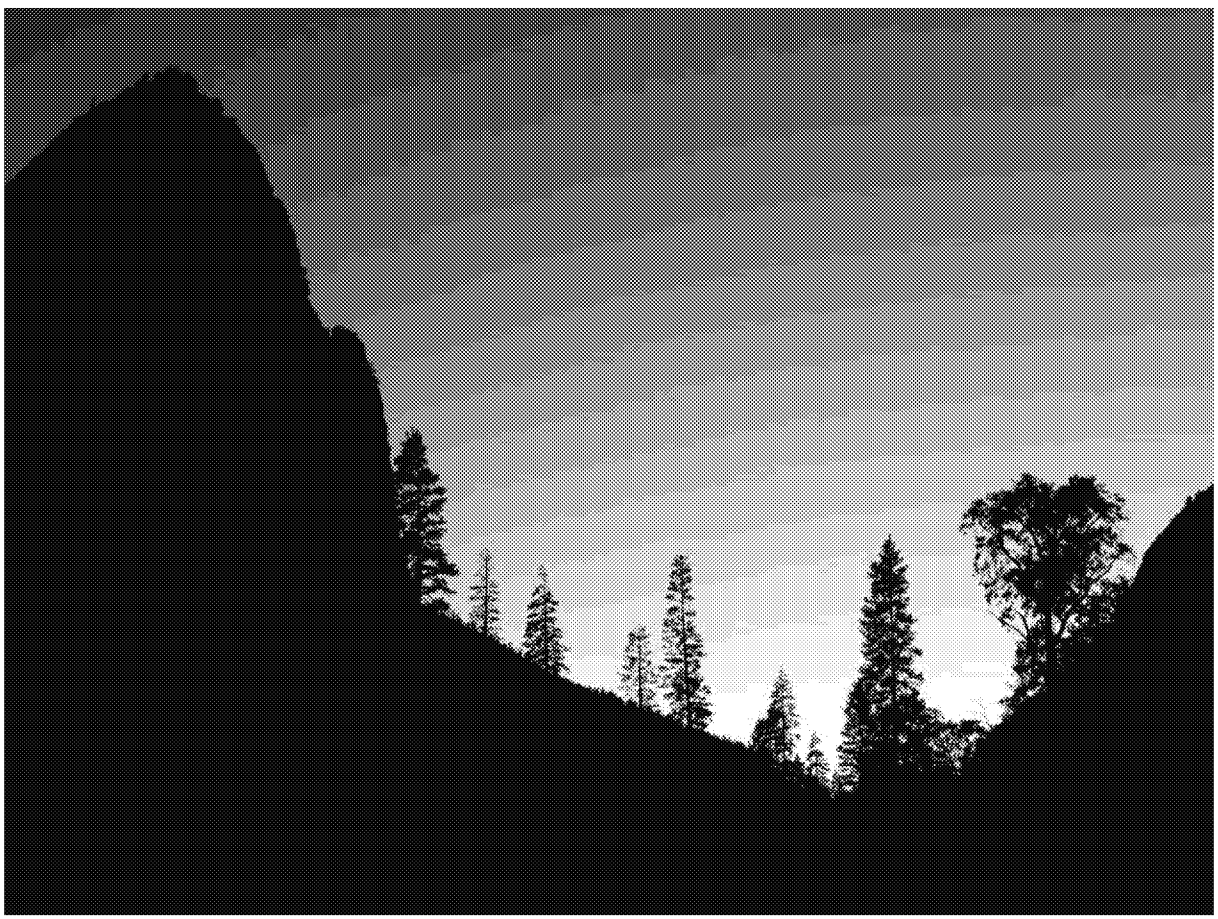
OMICS,

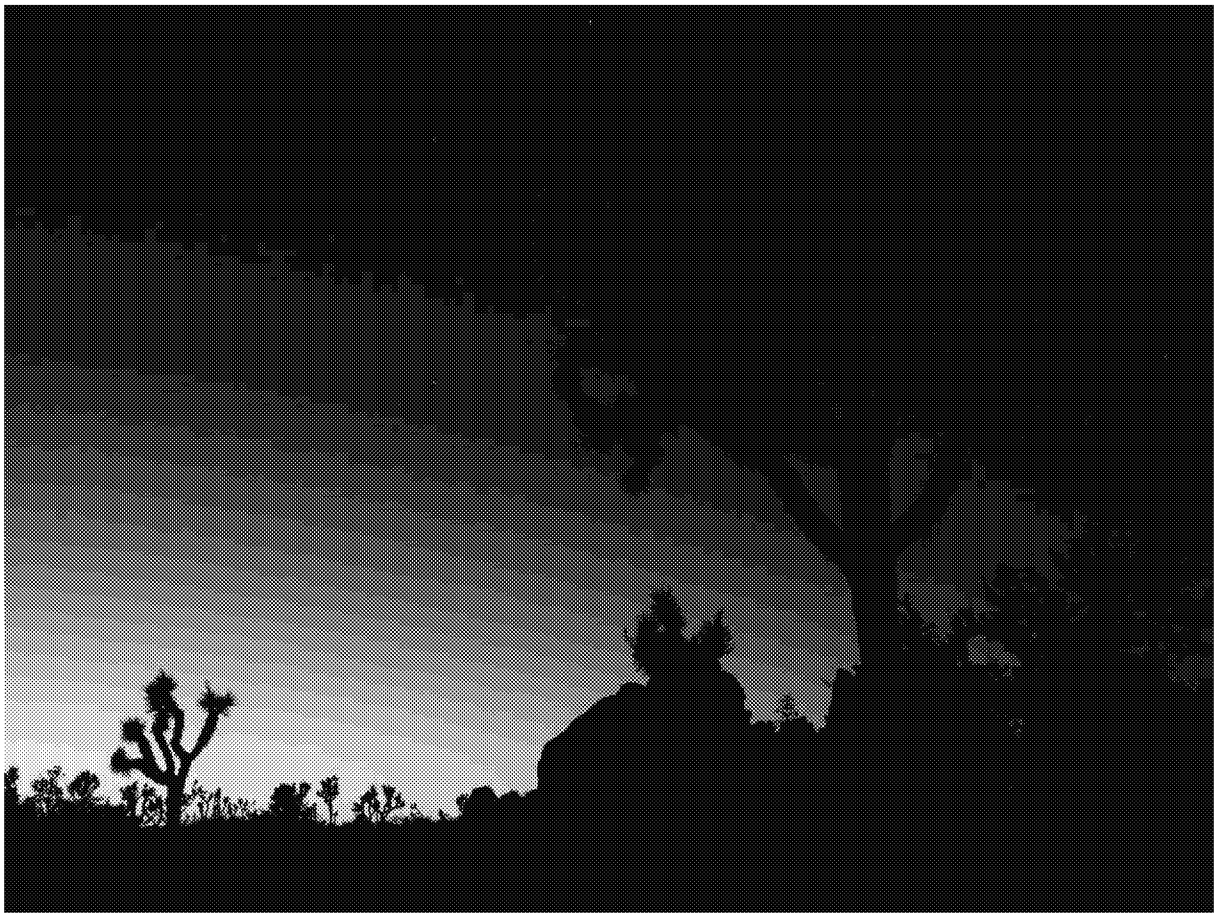
QSARs,

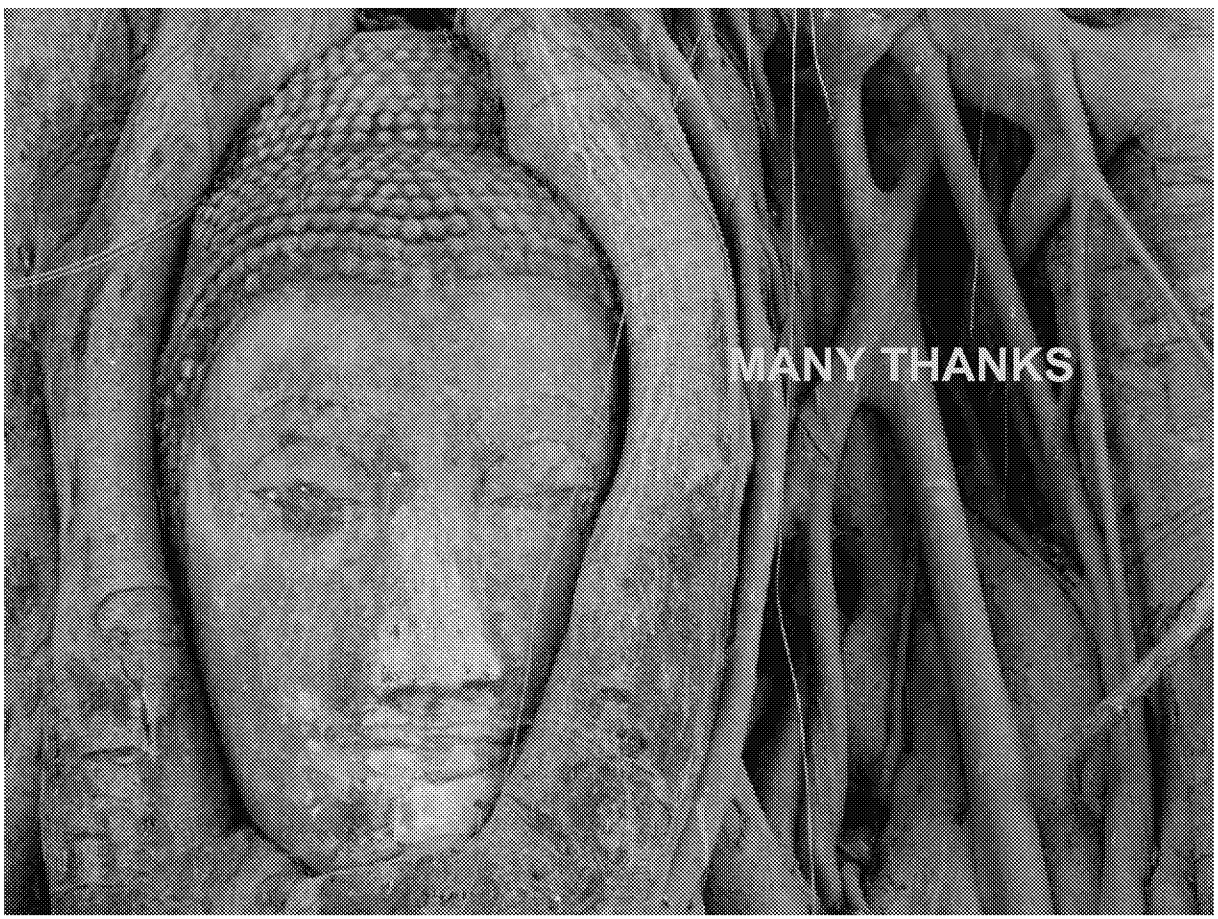
Mode of action (IPCS working group US-EPA, ECHA…)

PB-PK models and human variability data in metabolism








MANY THANKS

JECFA
Process, Rules and Principles

Dr. Angelika Tritscher
WHO Joint Secretary to JECFA and JMPR
Dept of Food Safety and Zoonoses (FOS)

World Health Organization

Outline

- Food Safety Risk Analysis Internationally
- Scientific Advice Activities Internationally
- JECFA
  - Roles and responsibilities
  - Rules and procedures
- Other Risk Assessment Activities

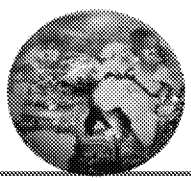
Risk Analysis Internationally

- Food standards are developed on the basis of scientific assessments
- Codex Standards are the international benchmark within WTO-SPS and TBT

JECFA
JMPR
JEMRA
Ad hoc

CAC
CCFAC
CCRVDF
CCPR
CCFH

World Health Organization



Role of Codex Standards

- WHO and FAO are not regulatory authorities
- Codex standards are recommendations – implementation is responsibility of national authorities
- WTO/Sanitary and Phytosanitary Agreement (SPS) is legally binding by signatories
- Codex standards are food safety benchmark within WTO/SPS
- Members may introduce higher level of measures than international standards;
  - if there is a scientific justification
  - if determined to be appropriate by risk assessment
- Highlights the importance of internationally harmonized scientific assessments for food safety

World Health Organization

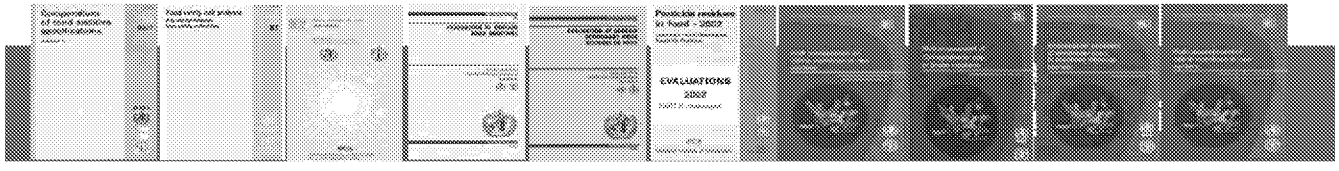
FAO/WHO Expert bodies

JECFA: Joint FAO/WHO Expert Committee on Food Additives
since 1956: 2600 food additives, 40 contaminants, 90 veterinary drugs

JMPR: Joint FAO/WHO Meeting on Pesticide residues
since 1963: 240 pesticides, several thousand max. residue levels in food

JEMRA: Joint FAO/WHO Expert meeting on Microbiological Risk Assessment
since 2000: Salmonella, Campylobacter, Listeria, Vibrio, Enterobacter

Ad-hoc Expert Consultations:
e.g. Risk Benefit of Fish, Antimicrobial Resistance, Bisphenol A, Melamine



JECFA: Areas of Work

- **Risk assessment/safety evaluation of:**
  - **Food Additives**
  - **Processing aids (considered as food additives)**
  - **Flavouring agents (by groups of related compounds)**
  - **Contaminants**
  - **Natural toxins**
  - **Residues of Veterinary Drugs in animal products**
- **Specifications and analytical methods, Residue definition, MRL proposals (veterinary drugs)**
- **Development and improvement of general principles**

World Health Organization

Codex Definition of FA

Food Additive means any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result, (directly or indirectly) in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods.

The term does not include "contaminants" or substances added to food for maintaining or improving nutritional qualities.

World Health Organization

JECFA : Procedure

CODEX Alimentarius Commission

FAO and WHO Member countries

Secretariat

ISSUES & PRIORITIES

The Joint Secretariat sets the agenda of JECFA

- **Call for data (12-10 mo before meeting)**
- **Selecting participants; preparation of working papers**
- **Meeting**
- **Report & Monographs**

World Health Organization

JECFA Output

REPORTS

- WHO Technical Report Series (TRS)
These reports, published by the World Health Organization, contain concise toxicological evaluations and the chemical and analytical aspects of each substance reviewed by JECFA, as well as information on the intake assessment. Reports reflect the agreed view of the Committee as a whole and describe the basis for their conclusions. They are available in PDF format, and the 1st through 36th reports are also available in French and Spanish.

TOXICOLOGICAL MONOGRAPHS

- WHO Food Additive Series (FAS)
These monographs, published by the World Health Organization, contain detailed descriptions of the biological and toxicological data considered in the evaluation, as well as the intake assessment. The 1st, 4th, 5th, 6th, 8th, 10th, and 12th through 52nd series of FAS monographs are available in HTML format. WHO monographs beginning with the 51st series are also available in PDF format.

- IPCS INCHEM database
Searchable database of all JECFA Monographs and other IPCS Risk Assessment documents.

- Database of evaluation summaries
JECFA maintains a searchable database containing summaries of all the evaluations of food additives, contaminants, toxicants and veterinary drugs it has reviewed. Each summary contains basic chemical information, ADIs, a history of JECFA evaluations and references to the most recent reports and monographs. The database allows searches for specific compounds, as well as searches by functional class. For an explanation of the database output, click here.

SPECIFICATIONS AND RESIDUES MONOGRAPHS

JECFA at WHO:
http://www.who.int/ipcs/food/jecfa/en/
JECFA at FAO:
http://www.fao.org/ag/agn/agns/jecfa_index_en.asp

World Health Organization

JECFA - Achievements

- Overall evaluations:
  - > 2600 food additives
  - > 40 contaminants
  - > 90 veterinary drugs
- Flavours Evaluation: application of TTC concept
- Genotoxic and carcinogenic contaminants: MoE
- Principles and Methods for the risk assessment of chemicals in food

World Health Organization

JECFA Risk Assessment Process

- Procedural guidelines:
  - WHO Procedural Guidelines
    http://www.who.int/entity/ipcs/food/jecfa/en/procedural_guidelines_additives.pdf
  - Guidelines for the preparation of toxicological working papers
    structure and outline of draft evaluation ('working paper')
    guidance and example on description and interpretation of studies
    http://www.who.int/entity/ipcs/food/jecfa/en/tox_guidelines.pdf
- Risk/safety assessment process:
  - Systematic evaluation of all available data
  - Submitted and published data (manufacturer, governments, scientific literature)
  - Taking overall database in weight-of-evidence approach into account, e.g. mechanistic studies inform the hazard assessment process (mode of action)

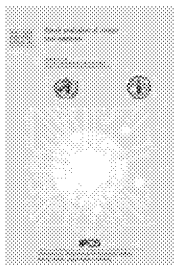
World Health Organization

JECFA Monographs Structure

1. Explanation .....
1.1 Chemical and technical considerations .....

2. Biological data .....
2.1 Biochemical aspects .....
2.1.1 Absorption, distribution and excretion .....
2.1.2 Bioavailability .....
2.1.3 Biotransformation .....

2.2 Toxicological studies .....
2.2.1 Acute toxicity .....
2.2.2 Short-term studies of toxicity .....
2.2.3 Long-term studies of toxicity and carcinogenicity .....
2.2.4 Genotoxicity .....
2.2.5 Reproductive toxicity .....
2.2.6 Special studies .....



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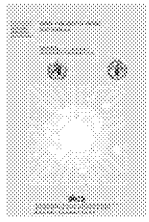
JECFA Monographs Structure (cont.)

2.3 Observations in humans .....
2.3.1 Clinical studies .....
2.3.2 Case-studies .....
2.3.3 Biomarker-studies .....



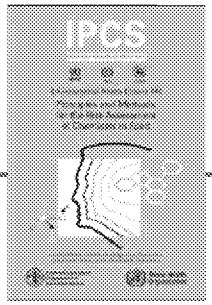
3. Dietary exposure .....
3.1 Use in foods .....
3.2 Dietary exposure estimates .....

4. Comments .....
4.1 Toxicological data .....
4.2 Assessment of dietary exposure .....

5. Evaluation .....

6. References .....

World Health Organization



Principles and Methods

EHC 240: Principles and methods for the assessment of chemicals in food, WHO 2009

- **Updated principles and methods**
- **Compiled all guidance developed by JECFA and JMPR since EHC 70 (1987) and EHC 104 (1990)**
- **Harmonize methods to the extent possible**

World Health Organization

EHC 240: Chapters

1. Introduction
2. Risk assessment and its role in risk analysis
3. Chemical characterisation, analytical methods, and the development of specifications

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4. Hazard identification and characterization: toxicological and human studies
5. Dose-response assessment and derivation of health-based guidance values
6. Dietary exposure assessment of chemicals in Food

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